



JC07 Rec'd PCT/PTO 19 MAR 2002
10/088400 \$

TRANSMITTAL LETTER TO THE UNITED STATES PATENT & TRADEMARK OFFICE ATTORNEY'S DOCKET NUMBER 0480/01219

DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09149	19 September 2000	24 September 1999

TITLE OF INVENTION: RATE-CONTROLLED PARTICLES

APPLICANT(S) FOR DO/EO/US Thomas HANTKE, Bettina REHBOCK, Joerg ROSENBERG, Joerg BREITENBACH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
 2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
 3. /X/ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
 4. /x/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
 5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b./ / has been transmitted by the International Bureau.
 - c./ / is not required, as the application was filed in the United States Receiving Office (RO/USO).
 6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
 7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
 - b./ / have been transmitted by the International Bureau.
 - c./ / have not been made; however, the time limit for making such amendments has NOT expired.
 - d./ / have not been made and will not be made.
 8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).
 9. / / An oath or declaration of the inventor(s)(35 U.S.C. 371(c)(4)).
 10. / / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11. to 16. below concern other document(s) or information included:
11. / / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
 12. / / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
 13. /X/ A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.
 14. / / A substitute specification.
 15. / / A change of power of attorney and/or address letter.
 16. /x/ Other items or information.
International Search Report
International Preliminary Examination Report

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0480/01219

a./X/ A check in the amount of \$890.- to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheet is enclosed.

Herbert B Keil

SIGNATURE

Herbert B. Keil

NAME _____

Registration No. 18,967

10/088400
JC1D Rec'd PCT/PTO 19 MAR 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of)
HANTKE et al.) BOX PCT
)
International Application)
PCT/EP 00/09149)
)
Filed: September 19, 2000)
)

For: RATE-CONTROLLED PARTICLES

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claims as shown on the attached sheets.

R E M A R K S

The claims have been amended to eliminate multiple dependency and to place them in better form for U.S. filing. No new matter is included.

A clean copy of the claims is attached.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF



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CLEAN VERSION OF AMENDED CLAIMS - 0480/01219

amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

1[4-[4-[4-[(4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl)methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-

CLEAN VERSION OF AMENDED CLAIMS - 0480/01219

4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxyl]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to a claim 1.

3. Particles according to claim 1 [or 2], further comprising a surfactant.
5. Particles according to claim 1 [any of the claims 1 to 3], wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.
6. Particles according to claim 1 [any of the claims 1 to 3], further comprising citric acid in amounts of up to 5% b.w.
7. Particles according to claim 1 [any of the claims 1 to 6], wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70% b.w. of the total weight of the dosage form.
9. Particles according to claim 1 [any of the claims 1 to 8], wherein the controlled release is an instant release of the drug.
10. Particles according to claim 1 [any of the claims 1 to 8], wherein the controlled release is a sustained release.
12. Particles according to claim 1 [any of claims 1 to 11], obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extrudate.
13. Particles according to claim 1 [any of the claims 1 to 11], comprising a compound selected from the group consisting of
4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]3,5-dimethylbenzonitrile;
4-[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-

MARKED VERSION OF AMENDED CLAIMS - 0480/01219

amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;

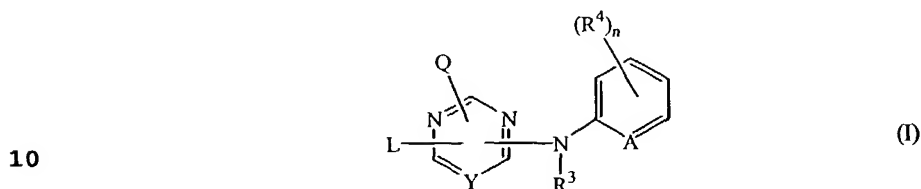
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

1[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-

1. Rate-controlled release particles, comprising a compound of
5 formula I

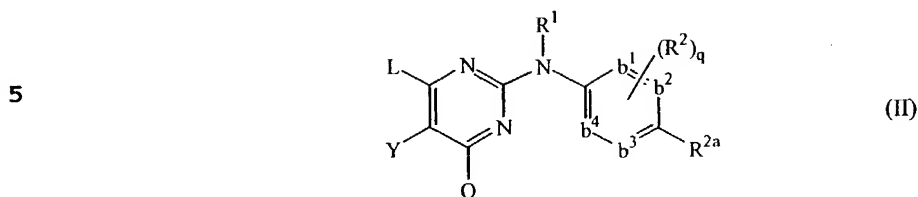


a N-oxide, a pharmaceutically acceptable addition salt or a
15 stereochemically isomeric form thereof, wherein

- 15 Y is CR⁵ or N;
A is CH, CR⁴ or N;
n is 0, 1, 2, 3 or 4;
Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;
20 R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may
25 optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or
30 R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;
R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyl-
35 oxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxy-carbonyl; and
each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyl-oxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also
40 represent C₁₋₆alkyl substituted with cyano or amino-carbonyl;
R⁵ is hydrogen or C₁₋₄alkyl;
L is -X¹-R⁶ or -X²-Alk-R⁷ wherein
45 R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

2

or a compound of formula



10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

- 15
- $-CH=CH-C(R^{2a})=CH-CH=$ (b-1);
 - $-N=CH-C(R^{2a})=CH-CH=$ (b-2);
 - $-CH=N-C(R^{2a})=CH-CH=$ (b-3);
 - $-N=CH-C(R^{2a})=N-CH=$ (b-4);
 - $-N=CH-C(R^{2a})=CH-N=$ (b-5);
 - $-CH=N-C(R^{2a})=N-CH=$ (b-6);
 - 20 $-N=N-C(R^{2a})=CH-CH=$ (b-7);

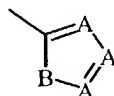
q is 0, 1, 2; or where possible *q* is 3 or 4;

*R*¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl;

25 *R*^{2a} is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C₁₋₆alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

30 each *R*² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or $-C(=O)R^6$, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula

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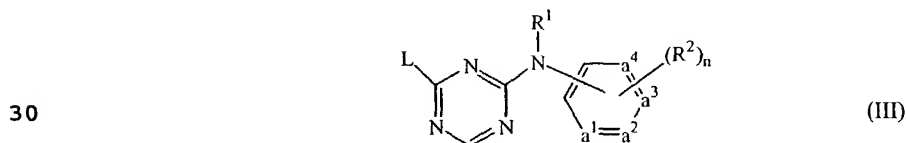


(c)

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- wherein each A independently is N, CH or CR⁶;
 B is NH, O, S or NR⁶;
 p is 1 or 2; and
 R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;
- 5 L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from
- 10 * C₃₋₇cycloalkyl,
 * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkyl-carbonyl,
- 15 * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or
- 20 L is -X-R³ wherein
 R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and
- 25 X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;
- Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and
- 30 R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl
- 35 wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or
- 40 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;
- 45

- Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or
- 5 -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;
- 10 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;
- Het is an aliphatic or aromatic heterocyclic radical;
- 15 said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said
- 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,
- 25 or a compound of formula



- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof,
- 35 wherein
- a¹=a²-a³=a⁴- represents a bivalent radical of formula
- CH=CH-CH=CH- (a-1);
- N=CH-CH=CH- (a-2);
- N=CH-N=CH- (a-3);
- 40 -N=CH-CH=N- (a-4);
- N=N-CH=CH- (a-5);
- n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;
- R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl,
- 45 C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

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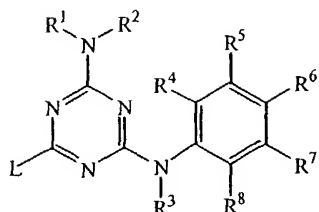
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or a compound of formula

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(IV)

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the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyc₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or

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20

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-alkylidene;

25

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

30

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

35

L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

45

	Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
5	a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
	b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
	c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
	d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
	e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
	f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
	g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
	h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
10	i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
	l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
15	m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
	n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
	o	Phenylmethyl	H/H	H	H	H	H	H	H

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30

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(V)

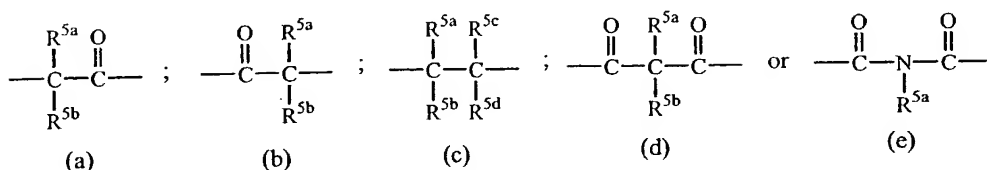
Chemical structure (V) is a complex molecule. It features a 1,3-dioxolane ring. At the 2-position of the dioxolane, there is a methylene group (-CH₂-) connected to a nitrogen atom (N) which is also bonded to an 'X' group. At the 4-position of the dioxolane, there is an ethyleneoxy chain (-O-CH₂-CH₂-O-) connected to a biphenyl system. The biphenyl system consists of two benzene rings connected by a piperazine ring. One of the benzene rings is substituted with a carbamate group (-N(R³)-C(=O)-N(R²)(R⁴)). The other benzene ring is substituted with a phenyl group and a group labeled (R¹)_n.

40

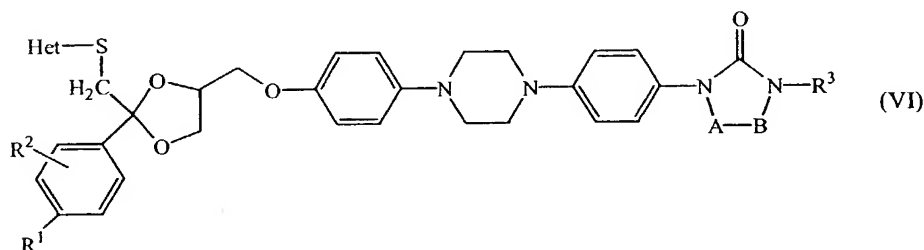
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R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

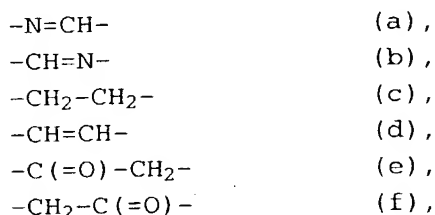
R^3 and R^4 each independently are hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; or
 R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:



wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and
 aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl,
 or a compound of formula



the N -oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

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amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-

pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-

yl]amino]benzonitrile;

1[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-

yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;

(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[2-(4-chlorophenyl)-2-[(4-methyl-4H-

1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxyl]phenyl]-1-

piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically

isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to a claim 1.
15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

JC10 Rec'd PCT/PTO 19 MAR 2002

Rate-controlled particles

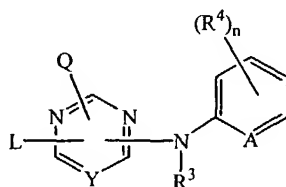
Specification

5

The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

10 (I) is an antiviral compound of formula

15



(I)

a N-oxide, a pharmaceutically acceptable addition salt or a
20 stereochemically isomeric form thereof, wherein

Y is CR⁵ or N;A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

25 Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

R¹ and R² are each independently selected from hydrogen,
hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl,
C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-
amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of
30 the aforementioned C₁₋₁₂alkyl groups may optionally and each
individually be substituted with one or two substituents each
independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-
C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino,
imino, aminocarbonyl, aminocarbonylamino, mono- or

35 di(C₁₋₆alkyl)amino, aryl and Het; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl,
morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-
alkylidene;

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-
40 carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and
each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy,
cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-
methyloxy, or when Y is CR⁵ then R⁴ may also represent
C₁₋₆alkyl substituted with cyano or aminocarbonyl;

45 R⁵ is hydrogen or C₁₋₄alkyl;L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

2

- R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;
- X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-;
- Alk is C₁₋₄alkanediyl; or
- when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C₁₋₆alkylcarbonyl;
- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl;
- Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (I) can be prepared according to the methods described in the patent applications with application number PCT/EP99/02043 and PCT/EP99/02044.

(II) is an antiviral compound of formula



$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

15

20

R1

25 R^{2a}

30

35



B is NH, O, S or NR⁶;

45

R⁶ is methyl, amino, mono- or dimethylamino or polyhalo-
methyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,

5 * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkylcarbonyl,

10 * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

15 L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and

20 X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;

Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

25 R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxy-carbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be

30 substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxy-carbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

35 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;

Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl

40 optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxy-carbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;

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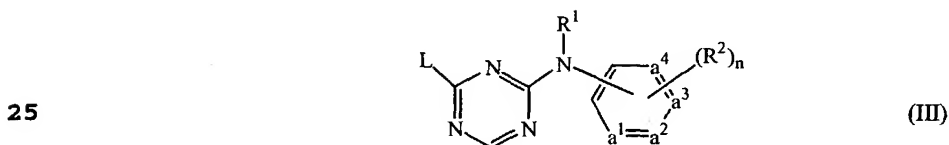
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

5 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted
10 with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

15

The compounds of formula (II) can be prepared according to the methods described in the US patent applications with application number 60/143962 and 60/107792.

20 (III) is an antiviral compound of formula



a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

30 $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

$$-\text{CH}=\text{CH}-\text{CH}=\text{CH}- \quad (\text{a-1});$$
$$-\text{N}=\text{CH}-\text{CH}=\text{CH}- \quad (\text{a-2});$$
$$-\text{N}=\text{CH}-\text{N}=\text{CH}- \quad (\text{a-3});$$
$$-\text{N}=\text{CH}-\text{CH}=\text{N}- \quad (\text{a-4}) ;$$

35 --N=N--CH=CH-- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is $(a-1)$, then n may also be 5;

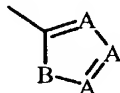
R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

40 C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and
each R² independently is hydroxy, halo, C₁₋₆alkyl optionally sub-
stituted with cyano or -C(=O)R⁴, C₃₋₇cycloalkyl, C₂₋₆alkenyl
optionally substituted with one or more halogen atoms or
cyano, C₂₋₆alkynyl optionally substituted with one or more
45 halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl,
carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino,

6

polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula

5



(c)

wherein each A independently is N, CH or CR⁴;

B is NH, O, S or NR⁴;

10 p is 1 or 2; and

R⁴ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C₄₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

15 one or two substituents independently selected from

* C₃₋₇cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy,

20 cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

25 tuents each independently selected from the substituents
defined in R²; or

L is $-X-R^3$ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R²; and

30 be substituted with two, three, four or five substituents
each independently selected from the substituents defined
in R²; and

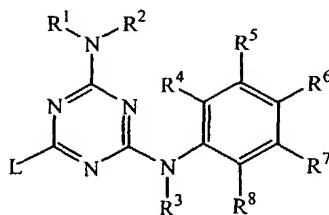
X is $\text{-NR}^1\text{-}$, -NH-NH- , -N=N- , -O- , -C(=O)- , -CHOH- , -S- , -S(=O)- or $\text{-S(=O)}_2\text{-}$;

35 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy.

40 The compounds of formula (III) can be prepared according to the methods described in the US patent application with application number 60/107799.

7

(IV) is an antiviral compound of formula



(IV)

10

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen; hydroxy;

amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyl-
 15 oxy carbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or
 di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl
 substituted with one or two substituents each independently
 selected from amino, imino, aminocarbonyl, aminocarbonyl-
 amino, hydroxy, hydroxyC₁₋₆alkyloxy, carboxyl, mono- or
 20 di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl,
 morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-
 alkylidene;

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-
 25 carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydro-
 gen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, amino-
 carbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

30 L is C₁₋₁₀alkyl substituted with one or two substituents
 independently selected from C₃₋₇cycloalkyl; indolyl or indolyl
 substituted with one, two, three or four substituents each
 independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy,
 cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-
 35 methyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted
 with one, two, three, four or five substituents each indepen-
 dently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy,
 cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-
 methyloxy, C₁₋₆alkylcarbonyl; and,

40 Ar¹ is phenyl, or phenyl substituted with one, two or three
 substituents each independently selected from halo, C₁₋₆alkyl,
 C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso
 that compounds (a) to (o)

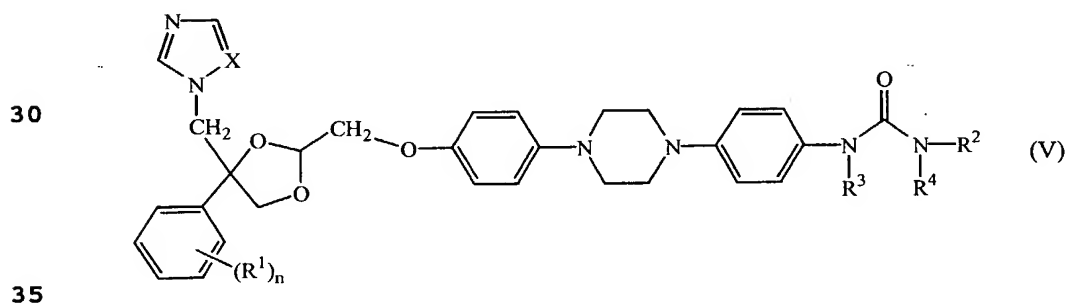
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	Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
5	a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
	b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
	c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
	d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
	e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
	f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
10	g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
	h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
	i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
15	l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
	m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
	n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
	o	Phenylmethyl	H/H	H	H	H	H	H	H

20 are not included.

The compounds of formula (IV) can be prepared according to the methods described in EP-A-0834507.

25 (V) is an antifungal compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein n is zero, 1, 2 or 3;

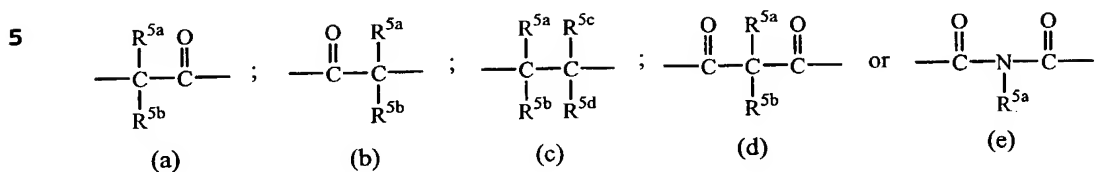
40 X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

R³ and R⁴ each independently are hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:



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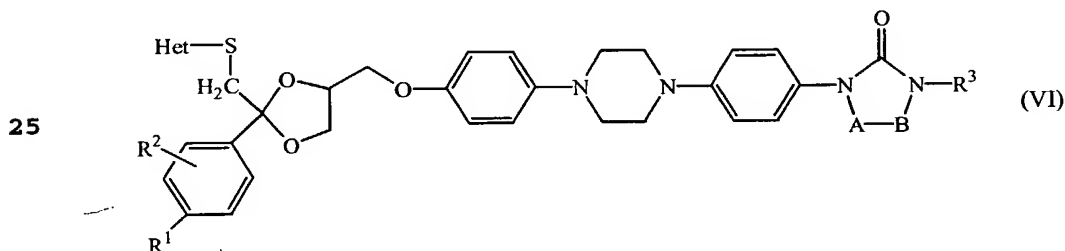
wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy,

15 C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl.

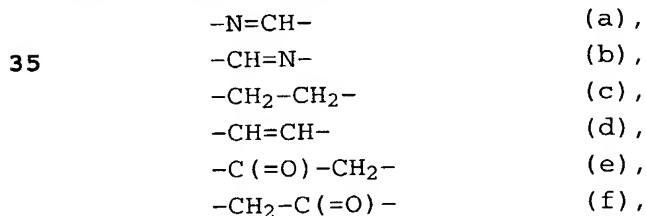
The compounds of formula (V) can be prepared according to the methods described in WO 99/02523.

20 (VI) is an apolipoprotein-B synthesis inhibitor of formula



30

the N -oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

45 R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

10

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine; 5 pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, 10 hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents 15 selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or 20 two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyl-oxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; 25 aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo.

The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

30 The compounds of formula (VI) can be prepared according to the methods described in WO 96/13499.

The particles comprise the compounds of formula (I) to (VI) as a solid dispersion in a polymeric matrix, wherein the poly-
35 meric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone. Furthermore, the invention concerns a process for manufacturing of such particles and pharmaceutical dosage forms comprising such particles.

40 The compounds of formula (I) to (VI) contained in the particles show poor bio-availability.

In order to improve the dissolution characteristics the compounds are dispersed in a polymeric matrix, preferably by using a melt-
45 extrusion process.

EP-A 0 240 904 discloses a method for producing solid pharmaceutical forms by extrusion of polymer melts which contain active substances, using as polymers homo- or copolymers of N-vinylpyrrolidone.

EP-B 0 580 860 discloses a method for producing solid dispersions of drug substances in a polymeric matrix using a twin screw extruder.

We have found that this object is achieved by the particles defined at the outset.

4-[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzo-
nitrile;

4-[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-
amino]benzonitrile;

30 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-
amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;

1-[4-[4-[4-[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;

- According to the present invention the term "rate-controlled" means that depending on the composition of the matrix the particles can show instant release of the active ingredient or modified release (sustained release).

The compounds according to the invention are homogeneously dispersed in a polymer matrix consisting of a homopolymer of N-vinylpyrrolidone or, preferably, a copolymer of N-vinylpyrrolidone. A preferred copolymer is a copolymer of N-vinylpyrrolidone and vinyl acetate, especially a copolymer obtained from 60% b.w. of NVP and 40% b.w. of vinylacetate.

- 20 The polymers show Fikentscher K values of from 17 to 90, preferably a K value of 30 (for the definition of the K value see "H. Fikentscher, Cellulose-Chemie" (1932), 58-64 and 71-74).

The polymeric matrix component is used in amounts of from 40 to 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

- In a preferred embodiment of the invention the polymeric matrix further comprises a surfactant, preferably a surfactant with a HLB-value of 10-18 (HLB: Hydrophilic Lipophilic Balance). Especially preferred surfactants are selected from the group consisting of low molecular weight polyoxyethylene polyoxypropylene block copolymers with a mean molecular weight of 1000 to 6000 g/mol, and hydrogenated castor oil which can be modified with polyethylene glycol.

The amounts of surfactants used lies in the range of up to 20% b.w., preferably 5 to 15% b.w., of the particles.

- 40 In another preferred embodiment the matrix further comprises an organic carboxylic acid in amounts of up to 5% b.w. of the particles.

In another preferred embodiment of the invention the polymeric matrix further comprises hydroxypropyl methyl cellulose in
45 amounts of up to 25% b.w., preferably from 5 to 10% b.w..

13

The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid
5 dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.

Such solid dispersion is preferably obtained by forming a homogeneous mixture of the components in the form of a melt,
10 extruding said melt and shaping of the extrudate. The melting is effected by the input of thermal and/or mechanic energy.

Depending on the composition of the matrix, the melting takes place in the range of from 40°C to 190°C, preferably 50 to 150°C.
15 The suitable temperature range depends on the glass transition temperature of the polymer component, the properties of the active ingredients and further additives. The optimal temperature range can be established by a few simple tests.

20 The mixing of the active substances with the polymer and additional components of the matrix can take place before or after the melting of the polymer. Preferably the process is solvent-free which means that no additional organic solvents or water are added.

25 The plastification and melting preferably can take place in an extruder, a kneader or a mixing reactor, preferably in an extruder having one or more screws which may rotate in the same direction or opposite directions, especially in a twin screw
30 extruder. The latter can be operated with or without kneading elements, but use of kneading elements is preferred because mixing is better.

The still plastic material is extruded through a die or a breaker
35 plate and then shaped into particles. This may be effected by milling and subsequent sieving the cooled extrudate. The preferred particle size for instant release forms lies in the range of from 0.5 to 1.5 mm.

40 The particles, optionally together with conventional pharmaceutically acceptable excipients, may be further processed to conventional pharmaceutical dosage forms such as tablets, pastilles, suppositories, or be packed in capsules.

45 It is possible and particularly advantageous to produce pharmaceutical forms with rate-controlled release and improved dissolution rates of the active ingredients. This was not to be

14

expected in view of the low solubility of the active ingredients in aqueous media.

Examples

5

General method

Powder mixes of the components were melt kneaded at 145°C for 5 min.. After cooling the solidified melts were ground and
10 sieved. The sieve fraction 0.5-1.5 mm was used for the dissolution tests.

The composition of the individual powder mixes is listed in Table 1.

15

Table 1

Example No.	1	2	3	4	5	6
Active ingredient ¹⁾	30	30	30	30	30	40
20 VP-VAC-copolymer ²⁾	65	55	55	60	55	47,1
Surfactant ³⁾	5	15		5	5	4,3
Citric acid				5		
HPMC					10	8,6
Surfactant ⁴⁾			15			

- 25 1) 4-[[4-[2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile
2) Kollidon® VA64, VP/VAC = 60/40, BASF Aktiengesellschaft
3) PEG-n-hydrogenated Castor oil
4) polyoxyethylene polyoxypropylene blockcopolymer, mean mol.
30 weight 4000 g/mol

The dissolution tests were carried out according to USP XXIII, paddle model, pH no change test, 0.1 M HCl, at 37°C, 100 rpm

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The results are listed in Table 2.

Table 2: Dissolution Rates of particles according to examples 1-6

5

	time [min]	Dissolution [%]				time [min]	Dissolution [%]	
		Ex. 1 (IR)	Ex. 2 (IR)	Ex. 3 (IR)	Ex. 4 (IR)		Ex. 5 (SR)	Ex. 6 (SR)
10	5	53	65	58	57	1		
	10	73	86	88	82	2		
	15	77	91	95	89	3		
	20	81	91	96	93	4		
	30	87	94	99	94	6		
15	60	92	93	96	94	8	96	95
	120	93	94	97	95			
		IR: Instant Release					SR: Sustained Release	

20 DSC-Measurements were performed with the formulations according to examples 1 to 6 in open pans (air) at temperatures of from 20 → 250°C, with a heating rate of 10°C per minute. There is no indication of crystalline drug substance in the solid dispersions.

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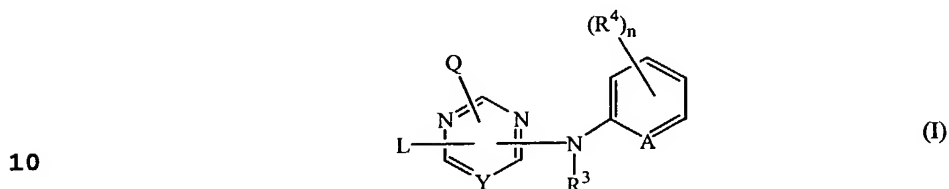
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Claims

1. Rate-controlled release particles, comprising a compound of
5 formula I



a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

- 15 Y is CR⁵ or N;
A is CH, CR⁴ or N;
n is 0, 1, 2, 3 or 4;
Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;
20 R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may
25 optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and
30 Het; or
R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;
R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxy-carbonyl; and
35 each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also
40 represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;
R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein
45 R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

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C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-; Alk is C₁₋₄alkanediyl; or when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C₁₋₆alkylcarbonyl; aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl; Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranlyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula



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wherein each A independently is N, CH or CR⁶;

p is 1 or 2; and

polyhalomethyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkyl-carbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

L is $-X-R^3$ wherein
 R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2 ; and

X is $\text{-NR}^1\text{-}$, -NH-NH- , -N=N- , -O- , -C(=O)- , -CHOH- , -S- , -S(=O)- or $\text{-S(=O)}_2\text{-}$;

Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

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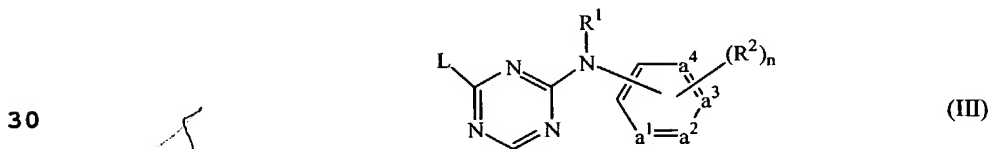
Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical;

said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula



a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

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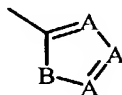
$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$	(a-1);
$-\text{N}=\text{CH}-\text{CH}=\text{CH}-$	(a-2);
$-\text{N}=\text{CH}-\text{N}=\text{CH}-$	(a-3);
$-\text{N}=\text{CH}-\text{CH}=\text{N}-$	(a-4);
$-\text{N}=\text{N}-\text{CH}=\text{CH}-$	(a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is $(a-1)$, then n may also be 5;

45 R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

21

each R^2 independently is hydroxy, halo, C_{1-6} alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7} cycloalkyl, C_{2-6} alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6} alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6} alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



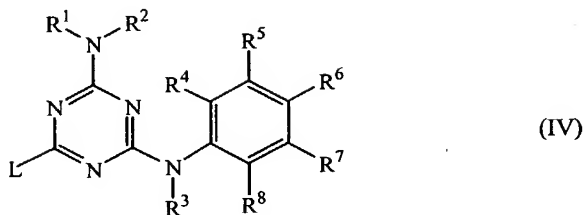
(c)

- wherein each A independently is N, CH or CR^4 ;
 B is NH, O, S or NR^4 ;
 p is 1 or 2; and
 R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;
- L is C_{4-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from
- * C_{3-7} cycloalkyl,
 - * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6} alkyl-carbonyl,
 - * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2 ; or
- L is $-X-R^3$ wherein
- R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2 ; and
- X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano, nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy,

22

or a compound of formula



10 the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

15 R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, amino-carbonyl, aminocarbonylamino, hydroxy, hydroxyC₁₋₆alkyl-oxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxy-carbonyl and thienyl; or

20 R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-alkylidene;

25 R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

30 R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

35 L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or
40 phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkyl-carbonyl; and,

45

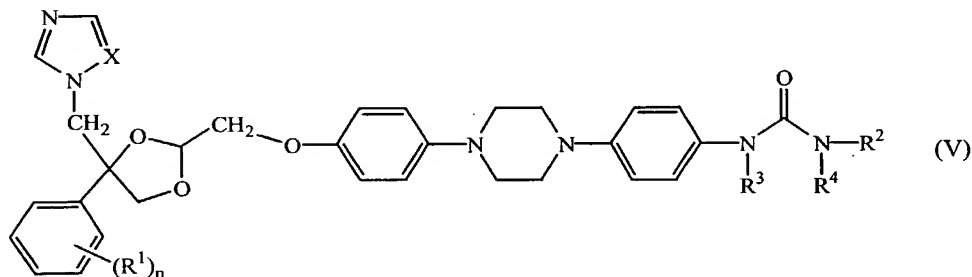
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Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

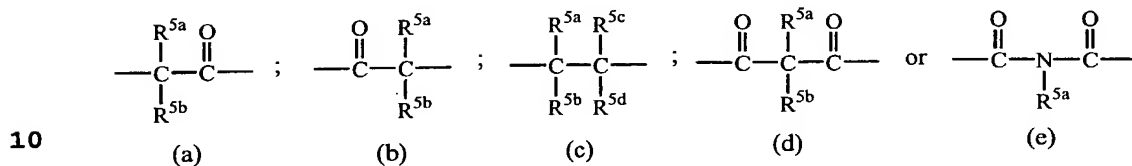
R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

24

R^3 and R^4 each independently are hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; or

R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

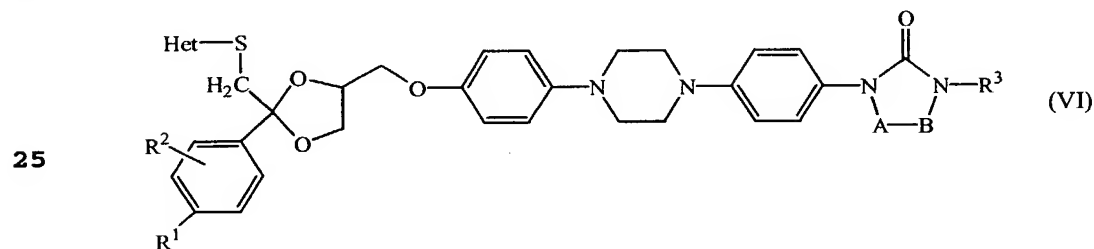
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15 wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl,

or a compound of formula

20



30 the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

- 35
- | | |
|----------------|------|
| $-N=CH-$ | (a), |
| $-CH=N-$ | (b), |
| $-CH_2-CH_2-$ | (c), |
| $-CH=CH-$ | (d), |
| $-C(=O)-CH_2-$ | (e), |
| $-CH_2-C(=O)-$ | (f), |

40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

45 R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

25

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

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Solution
as a solid ~~dispersion~~ in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.

35 2.

Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3.

Particles according to claim 1 or 2, further comprising a surfactant.

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4.

Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

5.

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Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

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6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.
7. Particles according to any of the claims 1 to 6, wherein the
5 homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.
8. Particles according to claim 7, wherein the homo- or copoly-
10 mer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..
9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.
- 15 10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.
11. Particles according to claim 10, further comprising hydroxy-
propyl methyl cellulose in amounts of from 5 to 10 % b.w..
- 20 12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extru-
date.
- 25 13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of
- 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-
benzonitrile;
- 30 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethyl-
benzonitrile;
- 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-
pyrimidinyl]-amino]benzonitrile;
- 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-
35 amino]benzonitrile;
- 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-
amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-
pyrimidinyl]amino]benzonitrile;
- 40 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-
pyrimidinyl]-
amino]benzonitrile;
- 4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-
pyrimidinyl]amino]benzonitrile;
- 45 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-
pyrimidinyl]amino]benzonitrile;

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4-[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-
amino]benzonitrile;

4-[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;

5 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

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10 (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[2-(4-chlorophenyl)-
2-[[4-(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-
-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-
(1-methyl-propyl)-3H-1,2,4-triazol-3-one,

15 a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.

20 15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

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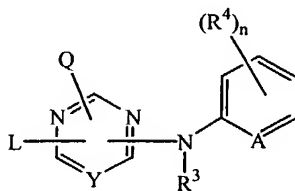
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Abstract

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(I)

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(74) Agent: GOLDSCHIED, Bettina; BASF Aktiengesellschaft, 67056 Ludwigshafen (DE).

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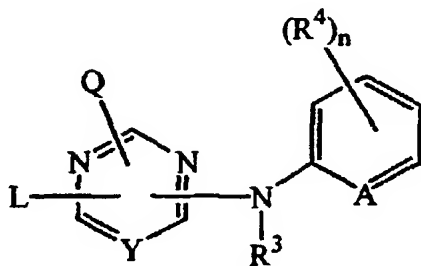
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RATE-CONTROLLED PARTICLES



(I)

(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

Declaration, Power of Attorney

Page 1 of 3

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Rate-controlled particles

the specification of which

☐ is attached hereto.

☒ was filed on May 19, 2002 as

Application Serial No. 10/088,400

and amended on _____

☒ was filed as PCT international application

Number PCT/EP00/09149

on 19 September 2000

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
199 45 982.7	Germany	24 Sept 1999	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.

Filing Date

Status (pending, patented,
abandoned)

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

2 -
And we (I) hereby appoint Messrs. **HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number 18,495; the address of both being Messrs. Keil & Weinkauff, 1101 Connecticut Ave., N.W., Washington, D.C. 20036 (telephone 202-659-0100), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

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